BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 : A61K 37/54, 37/48

A1

(11) International Publication Number: WO 84/ 02846

(43) International Publication Date: 2 August 1984 (02.08.84)

(21) International Application Number: PCT/US84/00079

(22) International Filing Date: 18 January 1984 (18.01.84)

(31) Priority Application Number: 460,023

(32) Priority Date: 21 January 1983 (21.01.83)

(33) Priority Country: US

(71) Applicant: ADVANCED DRUG TECHNOLOGY CORPORATION [US/US]; 9333 North Meridan Street, Indianapolis, IN 46260 (US).

(72) Inventor: BILTON, Gerald, L. ; P.O. Box 2345, Zionsville, IN 46077 (US).

(74) Agent: BIRDE, Patrick, J.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: ENZYME OINTMENT

(57) Abstract

A topical ointment for skin surface wounds comprising wound-healing amounts of papain, bromelain, trypsin, chymotrypsin, pancreatin, lipase, amylase, aloe extract and an organic astringent agent formulated in a carrier mixture of penetrating and non-penetrating emollient oils and a polyhydric alcohol emollient. The ointment reduces inflammation at the site of skin-surface wounds and acts to enhance the normal anti-inflammatory activities of the body.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BG	Bulgaria
BR	Brazil
CF	Central African Republic
CG	Congo
CH	Switzerland
CM	Cameroon
DE	Germany, Federal Republic of
DK	Denmark
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
HU	Hungary
IT	Italy
JP	Japan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
LI	Liechtenstein
LK	Sri Lanka
LU	Luxembourg
MC	Monaco
MG	Madagascar
ML	Mali
MR	Mauritania
MW	Malawi
NL	Netherlands
NO	Norway
RO	Romania
SD	Sudan
SE	Sweden
SN	Senegal
SU	Soviet Union
TD	Chad
TG	Togo
US	United States of America

ENZYME OINTMENT

BACKGROUND OF THE INVENTION

Injury to body tissues is immediately followed by acute local reaction characterized largely by a variety of vascular changes at the site of the injury. These changes include the outpouring of plasma fluids, proteins, and white blood cells, known collectively as exudate. This inflammatory response to injury is virtually identical regardless of the site of trauma in the body. See, Robbins & Angell, Basic Pathology 32 (2nd ed. 1976)

Certain prostaglandins, i.e. PGE, and thromboxanes are thought to be synthesized at the trauma site and are believed to be important mediators of the vascular adjustments to be made in the inflammatory response of the body. See, Robbins & Angell, Basic Pathology 38 (2nd ed. 1976). As the prostaglandin level increases, a series of changes occur at the trauma site. Platelet aggregation occurs, which is followed by the release of clotting factors such as fibrin and thrombin. There is a release of enzyme blocking factors which prevent fibrin dissolution and further strengthen the response. Smooth muscle contraction then leads to decreased vascular permeability, trapping excess fluid and necrotic debris within this fortified network. The body

eventually completely isolates the damaged area and the physical symptoms of edema, heat, erythema and pain become prevalent.

Thus, once subjected to trauma the body tends to isolate and "wall-in" at the trauma site exudate, necrotic debris, which is primarily protein in nature, and any entrapped bacteria and viruses, which are primarily composed of protein and lipids. Particularly in the case of acute trauma, which is prevalent with respect to skin-surface injuries, the accumulation of these substances may be substantial if there is a significant loss of tissue. When this situation occurs, the system is overwhelmed thereby retarding tissue repair.

Plasma proteins such as plasminogen and fibrinolysin and the hepatic anticoagulent heparin are usually able to control inflammation during normal homeostasis. When the system is overwhelmed, however, as in the case of acute trauma, additional aid is needed by the body to control and alleviate the symptoms of inflammation, since restoration of the damaged tissue cannot be initiated until inflammation is reduced.

The accumulation of white blood cells as part of the exudate, principally neutrophils and macrophages, is part of the body's response to alleviate the symptoms of inflammation. For instance, both neutrophils and macrophages contain an abundance of lysosomes containing proteolytic enzymes which are capable of digesting protein matter and bacteria. Moreover, the lysosomes of macrophages are known to contain large quantities of lipases, which are capable of digesting the thick lipid membranes of certain bacteria. See Guyton, Textbook of Medical Physiology 70 (5th ed. 1976).

These defenses, however, are often inadequate to

effectuate rapid healing, particularly in acute skin-surface wounds, when there are excessive quantities of proteins and liquids "walled off" from the rest of the body. Thus, while the human body does in fact utilize proteolytic and other enzymes to effectuate an anti-inflammatory response, the full potential of these and other enzymes in conjunction with other substances for the alleviation of skin-surface wound inflammation in a topical application has not heretofore been realized.

It is therefore an object of the present invention to provide compositions whereby effective wound-healing amounts of proteolytic and other enzymes, in conjunction with other wound-healing substances, may be topically applied to a skin-surface wound.

It is another object of the present invention to enhance the normal anti-inflammatory activity of proteolytic enzymes.

It is yet another object of the present invention to provide substances in a composition which act synergistically to reduce swelling and pain at the site of skin-surface trauma and degeneration.

Other objects and advantages of the invention will become apparent upon consideration of the accompanying disclosure.

BRIEF DESCRIPTION OF THE INVENTION

The compositions of the present invention are ointments comprising a carrier mixture of penetrating and non-penetrating emollient oils and a polyhydric alcohol emollient; the proteolytic and other enzymes papain, bromelain, trypsin, chymotrypsin, pancreatin, lipase and amylase; aloe extract; and an organic astringent agent. The carrier mixture, enzymes, aloe extract and the

organic astringent agent function synergistically so as to provide an effective wound-healing topical ointment.

DETAILED DESCRIPTION OF THE INVENTION

The general pathology of wound-processes involved in overt skin-surface degeneration (ulcers) and traumatic wounds (cuts, bruises, etc.) has been discussed hereinabove, along with the action of certain enzymes in the healing process.

The natural limitations of the human body in the healing process, however, creates a need to expedite healing thereby decreasing the discomfort experienced by the afflicted individual.

In this regard, the compositions of the present invention are formulated so as to deliver wound-healing amounts of proteolytic enzymes to the scarred or otherwise traumatized site, in conjunction with reparative quantities of an aloe extract, an organic astringent agent, lipase, amylase, and carrier emollient oils. The phrase "wound-healing" as used herein is intended to refer to the process of tissue repair and to the reduction of symptoms of inflammation present due to the body's response to the cellular disruption of skin-surface mammalian tissue which is either traumatic, as in the case of a burn or cut, or on the other hand, representative of a degenerative process, such as an ulcer.

As an essential ingredient, the compositions of the present invention include a plurality of proteolytic enzymes, which generally function to hydrolyze or to lyse proteins into their component amino acids, thereby providing these essential amino acids in nutritionally adequate amounts. Fibrolytic, proteolytic enzymes possess the added capacity to lyse or digest fibrin

clots at wound sites. This action tends to restore the free flow of blood through the circulatory system thereby accelerating the healing process at wound sites and minimizing the development of scar tissue.

Moreover, proteolytic enzymes are believed to aid in the prevention of blood platelet aggregation, to increase tissue permeability and to enhance the natural proteolytic and fibrinolytic activity of the blood. Proteolytic enzymes have also been implicated as inhibitors of the enzyme-blocking factors previously discussed. In effect, these anti-inflammatory agents are prostaglandin inhibitors. Thus, the compositions of the invention will comprise one or more of the proteolytic enzymes streptokinase, urokinase, trypsin, chymotrypsin, papain, bromelain and pancreatin. In a preferred embodiment, all of these enzymes except streptokinase and urokinase are contained in the composition.

Trypsin and chymotrypsin have been demonstrated to be successful in the dissolution of the clotting factor fibrin, necrotic tissue and proteinaceous exudates. When applied topically to post-thrombotic leg ulcers, they have shown remarkable success in accelerating the healing process. See, Gordon, The Use of Topical Proteolytic Enzymes in the Treatment of Post-thrombotic Leg Ulcers, Brit. J. Clin. Prac., 29, 143 (1975). Moreover, trypsin and chymotrypsin are thought to have a favorable influence on the inflammatory process in thromophlebitis. It is expected that streptokinase and urokinase would exhibit similar actions when applied topically in an active form, and may be used in addition to, or as replacements for, the trypsins.

While trypsin and chymotrypsin are often used in combination for the prevention and treatment of

inflammation from injury, each may be used in the formulation of the present invention without the other. Preferably, trypsin will make up about .025-2.5% by weight and chymotrypsin about .001-1% by weight of the compositions of the present invention and most preferably, about .05-1% and .002-.1%, respectively.

Papain has been reported to achieve excellent results in promoting the healing of wounds. See, Hwang & Ivy, A Review of the Literature on the Potential Therapeutic Significance of Papain, Annals N.Y. Acad. Science, 54, 161 (1951-52). Indeed, papain has demonstrated clinical efficacy as a local agent to debride or solubilize collections of proteinaceous materials in an anti-inflammatory role. See, Emele et al., The Analgesic-Anti-Inflammatory activity of Papain, Arch. Int. Pharmacodyn., 159, 126 (1966). Moreover, papain acts not only upon fibrinogen, the precursor of fibrin, and other proteins, but also to destroy certain bacteria and viruses which may be contained in the wound. See, Hwang & Ivy, A Review of the Literature on the Potential Therapeutic Significance of Papain, Annals N.Y. Acad. Science, 54, 161 (1951-52).

Papain is considered to be clinically efficacious in a topical application in removing clotted blood, purulent exudate and necrotic tissue from skin-surface wounds and ulcers. Preferably, papain will make up about .05-5% by weight of the compositions according to the invention and most preferably, about .1-2%.

It has been proposed that the proteolytic thiol-enzyme ("SH-enzyme") bromelain acts to selectively inhibit the biosynthesis of proinflammatory prostaglandins, such as the platelet-aggregating thromboxanes. The use of bromelain is indicated since the endogenous proteases such as circulating plasmin, trypsin, chymotrypsin, and

lipases are inhibited by trauma or exposure to excessive stress. Bromelain also acts on fibrinogen and fibrin to yield products similar to those formed by plasmin and which stimulate the biosynthesis of anti-inflamatory prostaglandins such as PGI_2. Indeed, it has been reported that the efficacious results achieved in reversing the inflammatory state may be a direct action of bromelain on the proteins, including fibrin, deposited at the trauma site. See, S.J. Taussig, Med. Hypth., 6, 99 (1980), and J.M. Miller et al. Exptl. Med. Surg., 22, 277 (1964).

Preferably, bromelain will make up about .05-5% by weight of the total enzyme component of the composition according to the invention and most preferably, about .1-2%.

The compositions of the invention will also preferably incorporate an amount of pancreatin, or of the individual primary enzymes incorporated therein, or of mixtures of the individual enzymes with pancreatin. Pancreatin primarily contains amylase, protease and lipase; digestive enzymes which act to break down dietary starch, protein and fat, respectively. Since pancreatic deficiency or overload is implicated in many situations involving wounds, it is believed that a supplemental amount of pancreatin is a beneficial adjunct to the administration of the fibrinolytic and anti-inflammatory enzymes. Pancreatin aids in the restoration of normal digestive processes, including the proper metabolism of fats, which is necessary for the achievement of effective plasma levels of anticlotting and antiinflammatory prostaglandins. Pancreatin and/or its component enzymes preferably comprise up to about .1-10% by weight of the compositions of the present invention, most preferably about .2-2%.

The compositions of the present invention will also preferably include topically wound-cleansing amounts of pancreatic digestive enzymes such as lipases and/or amylases, which are thought to effect the fats and carbohydrates contained in the structure of bacteria and viruses. For instance, many types of viruses possess an outer cell envelope composed of protein, lipid and carbohydrate constituents. Amylase and/or lipase, in conjunction with the proteolytic enzymes of the present invention, are thought to act synergistically to degrade the cell envelope and protein and lipid components of the virus particle so as to inactivate the pathenogicity of viruses contained in or entering the wound.

Similarly, the cell wall and membrane of many strains of bacteria are rich in proteins, carbohydrates and fats. Consequently, a topical application of the compositions of the invention are thought to act on the cell wall and membrane of the bacterial cell leading to the lysing of the microorganism with a consequent loss of virulence. In this manner, wound-healing is aided by the control of infectious microorganisms.

Preferably, the pancreatic digestive enzymes such as lipase and amylase will each make up about .01-5% of the compositions of the present invention and most preferably, about .05-1%.

In order to enhance the reparative qualities of the hereinbefore discussed enzymes, the compositions according to the invention may also include an aloe extract and an organic astringent agent.

The aloe extract, which is preferably incorporated as an aloe concentrate, e.g. aloe vera or aloe perryi concentrate, is thought to promote healing and has been applied as a soothing cream to skin-surface wounds,

burns and scar tissue. In addition to being a rapid penetrator of the various skin layers, the aloe extract contains enzymes which promote the removal of dead skin while stimulating the normal growth of living tissue. As defined herein, the term "aloe extract" refers to the inspissated juice of the aloe plant as well as to its dried concentrates which contain aloe-emodin, aloin or other active anthraquinone principles.

The preferable organic astringent agent is witch hazel, a herb substance which has demonstrated effectiveness as an astringent for the treatment of itching, skin irritations and burns. This compound acts to inhibit the pathological transcapillary movement of plasma protein thereby reducing inflammation, edema and exudation. Witch hazel has been used in an antiseptic capacity for the healing of wounds and for cleansing the skin surface.

The compositions of the present invention may also include one or more of a mixture of carrier emollients of a penetrating emollient oil, a non-penetrating emollient oil and a polyhydric alcohol emollient.

Preferably, the penetrating emollient oil will be ethoxylated lanolin. In addition to its skin softening properties, lanolin is known to be effective as a moisturizer and lubricant. The substance penetrates into the skin surface quickly and is quite beneficial when applied to skin-surface wounds since it acts to prevent a dressing from sticking to the wound. This effective penetrator also acts to replenish valuable lipids in the wound area. Other characteristics of lanolin are disclosed in U.S. Patent No. 2,478,820, the disclosure of which is incorporated herein by reference. Useful compounds of this type are formed by the condensation of about 10-80 moles of ethylene oxide per

mole of lanolin or by the linking of sorbitol and lanolin with a polyoxyethylene chain containing 10-80 moles of ethylene oxide.

Particularly useful compounds of this type are commercially available from ICI Americas, Wilmington, Del. as Atlas® G-1790 (20 moles of ethylene oxide/mole of lanolin), Atlas® G-1441 (40 moles of ethylene oxide linking sorbitol and lanolin) and Atlas® G-1471 (75 moles of ethylene oxide linking sorbitol and lanolin).

The preferred non-penetrating emollient oil is petrolatum, which is known to aid in restoring the natural texture of the skin surface. Unlike ethoxylated lanolin, petrolatum is a non-penetrating moisturizer and lubricant for the skin surface and as such, acts to aid in the topical action of the composition of the present invention.

The preferred polyhydric alcohol emollient is glycerin. Its main utility is in moisturizing the skin and providing a medium solvent. It is also reported to possess therapeutic uses such as its application to reduce corneal edema. See, Remington's Pharmaceutical Sciences, A. Ossol ed, Mack Pub., Boston, Mass. (16th ed. 1980) at page 1255.

The weight percent of the carrier emollients is substantially greater than that of any of the other components of the invention. Preferably, the carrier emollients comprise about 85-99% of the total weight of the compositions of the present invention and most preferably, about 93-97%.

The compositions of the present invention may also include one or more antibacterial preservatives, preferably from the C_1-C_4 lower alkyl benzoates such as

methyl and propyl paraben, each with a total weight percent in the compositions of about .025-1.5%, preferably.

The total weight percent of the components of the compositions of the present invention may be varied over a wide range. For example, the weight percent of all of the enzymes in the compositions is preferably about .2-20% and of just the proteolytic enzymes, about .2-15%. The weight percent of aloe extract preferably ranges from about .05-3% and the weight percent of the organic astringent agent preferably ranges from about .06-3%.

Thus, in a preferred embodiment of the composition according to the invention, the respective weight percents would be as follows: enzymes, .2-20%; aloe extract, 0.02-10%, or preferably .05-3%; organic astringent agent, .025-8%, or preferably .06-3%; petrolatum, 40-80%; ethoxylated lanolin, 5-30%; glycerine 5-30%, and preservatives .05-3%.

Preferably, the compositions of the present invention will be formulated such that the total enzyme component will comprise, by weight, papain, about 15-40%; trypsin, about 5-15%; chymotrypsin, about .2-.6%; bromelain, about 10-30%; pancreatin, about 30-50%; lipase, about 2-8%; and amylase, about 2-8%.

The wound-healing, reparative quality of the ointment may be effectuated by means of the method according to the present invention. The method comprises the topical administration of an effective amount of the hereinabove discussed compositions to traumatic or degenerative skin-surface wounds.

The ointments are typically prepared by first mixing the carrier emollients. A second homogeneous mixture of

enzymes and aloe extract is then slowly incorporated into a small amount of the carrier emollient mixture. The resultant paste is then added to the remainder of the carrier emollient mixture while mixing in a mixer. A second homogeneous paste, composed of the organic astringent agent and a small quantity of the carrier emollient mixture is then added to the mixer and mixing of all the components is continued until the composition begins to solidify. At this time, the composition is poured into a tube filling apparatus, pressure is applied and the ointment is tubed.

The invention will be further described by reference to the following detailed example.

EXAMPLE - ENZYME OINTMENT

A melt of 15,162 g of petrolatum, 4,364 g of ethoxylated lanolin and 3,509 g of glycerin was prepared in a stainless steel container. Small amounts of a second homogeneous mixture of 252 g of pancreatin, 153 g papain, 113 g of bromelain, 25 g of lipase, 25 g of amylase, 60 g of trypsin, 2.5 g of chymotrypsin and 42 g of aloe vera powder extract were added to small quantities of the melt in a 2 gallon stainless steel container. The resultant paste was added to a larger quantity of the melt while mixing until homogeneous in a "J.H. Day" mixer.

A second paste was made of 84 g of witch hazel extract and a small amount of melt. When the paste was homogeneous, it was added to the first paste with mixing. When the homogeneous mixture began to solidify, it was poured into a "Colton" tube filling machine and one ounce tubes were filled under 30 lbs. pressure.

The ointment of this invention has been used in the treatment of superficial wounds and bruises and has been

reported as effective for such applications in providing symptomatic relief. The recommended mode of application is to apply a thin layer of the ointment to the afflicted area and optionally cover with a sterile gauze dressing.

As a result of the present invention, a novel ointment for skin-surface wound-healing has been provided. Although a preferred embodiment of the principles of this invention has been described in detail herein, it should be realized that the same are not limited to the particular embodiments described and that modifications thereof are contemplated and can be made without departing from the broad spirit and scope of this invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A skin-surface, anti-inflammatory ointment comprising:

(a) a carrier emollient comprising a non-penetrating emollient oil, a penetrating emollient oil and a polyhydric alcohol emollient;

(b) a plurality of wound-healing proteolytic enzymes;

(c) an organic astringent agent; and

(d) an aloe extract.

2. The ointment according to claim 1, wherein the non-penetrating emollient oil is petrolatum, the penetrating emollinent oil is an ethoxylated lanolin and the polyhydric alcohol emollient is glycerin.

3. The ointment according to claim 1, further comprising amylase and lipase.

4. The ointment according to claim 1, wherein the organic astringent agent is witch hazel.

5. The ointment according to claim 1, wherein the plurality of proteolytic enzymes comprises trypsin, chymotrypsin, pancreatin, papain and bromelain.

6. The ointment according to claim 1 wherein the plurality of enzymes comprises streptokinase, urokinase and mixtures thereof.

7. The ointment according to claim 5, wherein the plurality of proteolytic enzymes comprises about .2-15% by weight of the ointment.

8. The ointment according to claim 1, wherein the carrier emollient comprises about 93-97% by weight

of the ointment.

9. A skin-surface, anti-inflammatory ointment comprising:

(a) about .1-2% papain;
(b) about .1-2% bromelain;
(c) about .2-2% pancreatin;
(d) about .05-1% trypsin;
(e) about .002-.1% chymotrypsin;
(f) about .05-1% lipase
(g) about .05-1% amylase
(h) about .05-3% aloe vera powder extract;
(i) about .06-3% witch hazel;
(j) about 40-80% petrolatum;
(k) about 5-30% ethoxylated lanolin; and
(l) about 5-30% glycerin.

10. The ointment according to claim 8, further comprising about .05-3% of antibacterial preservative.

11. The ointment according to claim 3 wherein lipase comprises about .05-1% and amylase about .05-1% by weight of the ointment.

12. The ointment according to claim 1, wherein aloe extract comprises about .05-3% by weight of the ointment.

13. A method for alleviating the symptoms of a skin-surface wound by topically administering an effective amount of the ointment of claim 1.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US84/00079

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Intl. Cl.[3] A61K 37/54 & 37/48 U.S. Cl. 424/94

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/94

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Chemical Abstracts, Vol. 76-98 (1972-1983)
"Inflammation" "Enzyme"

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	US, A, 3,932,618, published 13 January 1976 Fujii	1-13
Y	US, A, 3,892,853, published 1 July 1975 Cobble	1-13
Y	US, A, 4,361,551, published 30 November 1982 Galbraith	1-13
Y	US, A, 2,917,433, published 15 December 1959 Goldman	1-13
Y	US, A, 3,878,197, published 15 April 1975 Maret	1-13
Y	N, Chemical Abstracts, Vol. 72, published 1970, Abstract No. 136409j	1-13
Y	U.S. Dispensatory of U.S.A. (Osol & Farrar) published 1955, pages 612, 633, 1024 and 1025	1-13

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
9 April 1984	23 APR 1984
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	Sam Rosen

Form PCT/ISA/210 (second sheet) (October 1981)